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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,254	12/06/2000	Augusto Inventi Solari	P101615 -0000	8796

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EXAMINER	
MOORE, WILLIAM W	
ART UNIT	PAPER NUMBER
1652	11

DATE MAILED: 06/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/673,254	Applicant(s) SOLARI ET AL.	
	Examiner William W. Moore	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to each of the prior applications in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). Currently, different application data sheets in the file state different priority documents and the specification has no first sentence making reference to either, or both, priority document(s). Applicant may also wish to request a Corrected Filing Report.

Information Disclosure Statement

Applicant's Information Disclosure Statement, Paper No. 5 filed December 6, 2000, is hereby acknowledged. A document, WO 89/11532, discussed in the International Preliminary Examination Report of Applicant's corresponding PCT application but not listed in the Search Report, is made of record herein on the accompanying PTO-Form 892.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claims 1-5, 7-12 and 14-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over either of Inventi et al., U.S. 5,695,966, or Dickens et al., 1996, and Stassi et al., WO 97/06266, all made of record with Applicant's Information Disclosure Statement, in view of any among Hwang et al. or Kaur, made of record with Applicant's Information Disclosure Statement, or Caruso et al., WO 89/11532, made of record herewith.

These claims presented in Applicant's priority PCT application were not amended in this national stage application, thus this rejection recapitulates the corresponding statement in the International Preliminary Examination Report [IPER]. Inventi et al. and Dickens et al. both teach the identification and isolation of a streptomycete genomic DNA comprising a *dox*A gene encoding a C-14 hydroxylase, an element required by claim 1 herein, that acts on daunorubicin [daunomycin] to produce doxorubicin. Inventi et al. and Dickens et al. further teach that they inserted the *dox*A gene into a plasmid expression vector in operable linkage with strong promoter, as required by claim 2 herein, and transformed *Streptomyces* host cells with the vectors wherein the cells prior to transformation could either produce or not produce daunorubicin, but were incapable of producing doxorubicin, as required by claims 14-17 herein, in order to conduct the biosynthetic processes required by claims 18 and 19 herein. See, Examples 1 and 2 of Inventi et al. and pages 3391-3394 of Dickens et al. The teachings of Dickens et al. are present in the corresponding PCT publication, WO 97/44439, made of record with Applicant's Information Disclosure Statement herein and similarly discussed in the IPER. Both Inventi and Dickens et al. characterize the cloned *dox*A genes, teaching that each encodes a cytochrome P450-like polyketide hydroxylase that converts daunorubicin to doxorubicin. Inventi et al. more particularly teach, see Figure 1, the 2.9kb *Bam*HI-*Sph*I restriction endonuclease segment comprising an internal 1269-nucleotide sequence encoding a DoxA product required by claims 7 and 8 herein, and Dickens et al. teach an internal 1269-nucleotide sequence encoding a DoxA product nearly identical in its amino acid sequence to that of the DoxA product of Inventi et al.

Because neither Inventi et al. nor Dickens et al. used the *Saccharopolyspora erythraea* *erm*E* promoter in an expression plasmid, the teaching of Stassi et al. that this promoter should be incorporated in expression plasmids to promote the high level expression of polyketide hydroxylases, see Examples 3, 5, 7 and 8 at pages 11-16 of Stassi et al., in actinomycete host cells generally, including *Streptomyces* species, is now cited and combined with the teachings of Inventi et al. and Dickens et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the *erm*E* promoter for the promoters used by either Inventi et al. or Dickens et al. in an expression plasmid comprising a *dox*A gene because Stassi et al. teach that operably linking the *erm*E promoter in an expression plasmid to a gene encoding a polyketide hydroxylase makes the plasmid better suited for high-level expression of the hydroxylase in a *Streptomyces* host cell, as required by claims 2, 3 and 13 herein.

Because none of Inventi et al., Dickens et al., nor Stassi et al. teach the identification or isolation of any daunorubicin and/or doxorubicin resistance genes, or suggest the use of such genes in a transformed host cell in a process for producing doxorubicin, the teachings of Hwang et al., Kaur, and Caruso et al. are now cited and combined with the teachings of Inventi et al., Dickens et al. and Stassi et al. Each of Hwang et al., Kaur, and Caruso et al. teach the identification and isolation of such resistance genes, the *drr*A and *drr*B genes, and the incorporation of these genes in expression plasmids, the transformation of *Streptomyces* host cells capable of producing doxorubicin with these plasmids to confer a doxorubicin-resistant phenotype on the host cells, and the practice of a resulting recombinant process for producing higher levels of doxorubicin than would be possible without transformation with the resistance genes. **See**, Figures 1 and 2 and accompanying disclosures at pages 8-13 of Caruso et al., inherently disclosing the *Xba*I-*Hin*dIII restriction endonuclease segment required by claim 9 herein. **See also**, Figures 1-4, 6, and 7 and accompanying disclosures

at pages 572-575 of Kaur. **See additionally,** Figures 2 and 3, Table 1, and disclosures at pages 1616-1619 of Hwang et al.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a DNA molecule comprising either of the *dox*A genes taught by Inventi et al. or Dickens et al., wherein said *dox*A gene is linked to the high efficiency *erm*E* promoter taught by Stassi et al., and to further comprise within the molecule, according to claims 1-5 herein, either or both of the *drr*A and *drr*B doxorubicin resistance genes taught by Hwang et al., Kaur, and Caruso et al., to prepare plasmids that comprise the DNA molecule and to prepare *Streptomyces* host cells transformed with the plasmid expression vector according to claims 10-12 and 14-17 herein, in order to conduct the doxorubicin biosynthetic processes of claims 18 and 19 herein. This is because the prior art teaches that increasing production of doxorubicin in a host cell results in increased toxicity to the host cell by the product and that such toxicity can be relieved by instituting or augmenting doxorubicin resistance by conferring the phenotype of resistance conveyed by transformation of the host cells with plasmids expressing either of both of the *drr*A and *drr*B doxorubicin resistance genes.

Claims 6 and 13 are rejected under 35 U.S.C. §103(a) as being unpatentable over Inventi et al., Dickens et al., Stassi et al., and Caruso et al., as applied to claims 1-5, 7-12, and 14-19 above, and further in view of Lomovskaya et al., also made of record with Applicant's Information Disclosure Statement.

Claims 6 and 13 presented in Applicant's priority PCT application were not amended in this national stage application, thus this rejection also recapitulates the corresponding statement in the IPER. Lomovskaya et al. teach the identification and isolation of the *drr*C gene, which also confers resistance to doxorubicin. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a DNA molecule comprising the *drr*C gene taught by Lomovskaya et al. according to claim 6 herein and to further prepare an expression plasmid comprising this *drr*C gene of claim 13 herein, in

order to transform *Streptomyces* host cells with the plasmid expression vector to conduct the doxorubicin biosynthetic processes of claims 18 and 19 herein. This is because the prior art in general teaches that increasing production of doxorubicin in a host cell results in increased toxicity to the host cell by the product and that such toxicity can be relieved by instituting or augmenting doxorubicin resistance by conferring doxorubicin resistance, a phenotype that can be conveyed by transforming the host cells with plasmids expressing a *drr*C doxorubicin resistance gene.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 7:00AM-5:30PM EST on Mondays and Wednesdays, between 7:00AM-1:30PM EST on Tuesdays and Thursdays, and between 8:30AM and 5:00PM EST on Fridays. **The examiner's direct FAX telephone number is 703.746.3169.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
June 25, 2002

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